No. 03-1237

IN THE
Supreme Court of the United States

MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. AND THE BURNHAM INSTITUTE,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR PETITIONER

DONALD R. DUNNER
THOMAS H. JENKINS
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.
901 New York Avenue, N.W.
Washington, D.C. 20001
(202) 408-4000

E. JOSHUA ROSENKRANZ
Counsel of Record
M. PATRICIA THAYER
JAMES N. CZABAN
GINA M. PARLOVECCHIO
NISHITA DOSHI
HELLER EHRMAN WHITE & MCAULIFFE LLP
120 West 45th Street
New York, NY 10036
(212) 832-8300

February 15, 2005

QUESTION PRESENTED

To expedite the marketing of pharmaceuticals upon expiration of relevant patents, Congress amended the patent laws in 1984 to insulate drug research from charges of infringement so long as the research is "reasonably related to the development and submission of information" to the Food and Drug Administration. Does this FDA safe harbor protect the animal and test-tube studies that typically accompany an application to the FDA to allow a new drug to proceed to clinical trials with humans?

PARTIES TO THE PROCEEDINGS BELOW

In the Court of Appeals and on the Petition for Writ of Certiorari, the caption included Telios Pharmaceuticals, Inc., an original plaintiff. Telios Pharmaceuticals, Inc. was dismissed as a party in the District Court. The cover of this brief reflects the correct caption. The Rule 29.6 Statement accompanying the Petition for Writ of Certiorari is otherwise accurate.

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The opinion of the U.S. Court of Appeals for the Federal Circuit is reported at 331 F.3d 860, *see* P.A. la-35a,[1] but the official published opinion does not include an "Errata" sheet issued by the court upon denial of Merck's petition for rehearing en banc, *see* P.A. 36a-37a. The electronic versions of the opinion incorporate the errata. *See* 2003 U.S. App. Lexis 27796. The District Court opinion reviewed by the Court of Appeals is not published. P.A. 47a-50a; *see also* Tr. 3375-91 (denial of pre-verdict JMOL).

JURISDICTION

The Court of Appeals entered judgment on June 6, 2003, and denied rehearing and rehearing en banc on December 3, 2003. The jurisdiction of the Court of Appeals was based on 28 U.S.C. §1295(a)(1). Merck filed its petition for a writ of certiorari on March 2, 2004, and this Court granted the petition on January 7, 2005. This Court's jurisdiction is invoked under 28 U.S.C. § 1254(1).

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[1] The Appendix to the Petition for Writ of Certiorari is cited as "P.A.," and the Joint Appendix and Supplemental Joint Appendix are cited as "J.A." and "S.A.," respectively. The trial transcript is cited as "Tr.," and trial exhibits and deposition exhibits (introduced into the record at trial), to the extent they are not reproduced in the appendices, will be cited as "T. Ex." and "D. Ex.," respectively. Documents on the District Court docket are cited as "Docket # ___."

STATUTORY PROVISIONS & REGULATIONS

The primary statutory provision relevant to this proceeding is the FDA exemption, found at 35 U.S.C. § 271(e)(1) (2000), which provides:

> It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other process involving site specific genetic manipulation techniques) solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

Also at issue are various statutory provisions and regulations governing the FDA. The following provisions are excerpted in the Appendix at the end of this brief: 21 U.S.C. § 355 (2000 & Supp. 2001); 21 C.F.R. §§ 58.3, 312.22-312.23, 314.50 (2004).

INTRODUCTION

This case was brought by the owner and licensees of aging patents purporting to cover a family of chemical compounds and certain uses of them. They had failed to find any commercial use for the patented inventions—and the original licensee went bankrupt trying. Merck KGaA ("Merck") discovered a brand new member of the family and, in collaboration with The Scripps Research Institute ("Scripps") in La Jolla, California, developed several groundbreaking therapeutic applications for it, including a

promising cancer treatment that is currently being tested in cancer patients. Merck did not market, or otherwise commercially exploit the drug it discovered, and will not do so before the patents expire. Rather, this lawsuit contends only that Merck violated the patents by sponsoring experiments at Scripps directed at establishing to the FDA's satisfaction that the new drug and a nearly identical analog were promising enough and safe enough to proceed to clinical trials in humans.

When Scripps was conducting the research, every court that had ever addressed the issue, as well as the research community, considered those sorts of experiments immune from patent infringement suits under the so-called "FDA exemption," which provides that: "It shall not be an act of infringement to . . . use . . . a patented invention . . . solely for uses reasonably related to the development and submission of information" to the Food and Drug Administration ("FDA"). 35 U.S.C. §271(e)(1) (2000). The statute's plain language embraces any information that a drug innovator could reasonably expect to submit to the FDA in connection with *any* application. And a drug innovator could never proceed with clinical trials on a new drug without submitting an application to the FDA—with extensive data from animal and test-tube studies—proving both that the drug has promising therapeutic effects and that it appears to be safe for human consumption.

The Court of Appeals, reversing an understanding that had prevailed for nearly two decades, held that the statute does not mean what it says. Rather, according to the court below, the words Congress chose must be severely limited by congressional "purposes" it gleaned from the legislative history. According to the Court of Appeals, Congress intended to protect mainly generic drugs that mimic drugs already on the market, but not the development of pioneering new drugs that may be more effective in curing disease than

any drug currently on the market. To the extent that the FDA exemption covers new drugs at all, the Court of Appeals continued, it covers only the final stage in the FDA approval process—the clinical testing on humans—and not the research in animals and test tubes that is a prerequisite to clinical trials.

If the Court of Appeals' opinion is upheld, the patent laws would allow the holder of a patent on a chemical to enjoin a medical researcher from conducting studies on animals that simulate human disease and that could yield ground-breaking cures for people. The patent holder would be able to bar all laboratory tests using the compound—or, as in this case, any structurally similar compounds—even though any new drug developed by the medical researcher would not be marketed until after all relevant patents expire. Drug innovators and researchers will have to sit on their hands awaiting patent expiration before *starting* to conduct the battery of experiments necessary to qualify a potentially path-breaking new drug for clinical trials involving human subjects, which, in turn, take many years to complete. Consequently, the patent holder will enjoy a de facto patent-term extension, while potential treatments for innumerable diseases and conditions will be denied to patients for a decade or more after all patents expire.

The Court of Appeals' ruling does not just defy the dreams of suffering patients. It defies settled expectations. It defies common sense. Most important of all, it defies congressional will, as expressed in the plain language of the statute Congress passed two decades ago to protect exactly the sorts of experiments now before the Court.

STATEMENT OF FACTS

The FDA Drug Approval Process

Because both the facts of this case and the legal analysis unfold against the backdrop of the FDA's regulatory regime for drugs, a primer on the drug development process and the FDA's application process is warranted by way of introduction.

New drugs vs. generics. The approval process depends upon whether the drug is a generic drug or a new drug, also called a "pioneer drug."[2] *Compare* 21 C.F.R. § 314.50 *with id.* §§ 314.92-314.94; *see generally* DONALD O. BEERS, GENERIC AND INNOVATOR DRUGS, A GUIDE TO FDA APPROVAL REQUIREMENTS § 1.01, at 1-2 to 1-7 (5th ed. 1999) (explaining regulatory regime). Generally, a new drug is different from any drug that is already being administered to patients. It might prevent or cure a disease that no other drug can. It might be more effective at curing a disease or relieving symptoms than other drugs on the market. Or it might have fewer or less severe side effects. The primary value of a new drug lies in its novelty, its unique life-saving, disease-curing, or palliative effects.

In contrast, generic drugs are mimics of drugs already on the market. *See* 21 U.S.C. § 355(j)(2)(A)(i)-(iv). By definition, they have no new curative properties; they are

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[2] Technically, under the statute, generics constitute a subset of new drugs that is subject to an abbreviated regulatory process. *See* 21 U.S.C. § 355(j). This brief adopts the common parlance, which the Court of Appeals followed, of treating new drugs and generics as distinct categories.

neither safer nor more effective than the drug patients are already taking. Their promoters cannot claim that they will save more lives or enhance the quality of life for any patient. The generic drug's main societal value is to enhance price competition. *See generally* Congressional Budget Office, *How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry* xiii (July 1998), *available at* ftp://ftp.cbo.gov/6xx/doc655/pharm.pdf.

The difference between new drugs and generics translates into a marked difference in regulatory requirements—and, specifically, in the information that must be presented to the FDA en route to FDA approval for commercial sale.

New drug development & regulatory approval. At issue in this case is a new drug Merck is developing—a drug with demonstrated potential to combat cancer and other diseases. J.A. 73-74, 77-78.

The idea for a new drug like Merck's emerges from years of basic research, research into the agents that cause disease and how the body's cells, tissues, and organs react to them. *See* J.A. 381-86; S.A. 1-2. As the basic research unmasks the disease's mysteries, and identifies the specific biochemical targets that play a role in the disease, ideas percolate about the properties of possible drugs that might interact with those targets to treat or prevent the disease. J.A. 381-86. Researchers may conduct "high-throughput screenings," testing the activity of thousands, even tens of thousands, of possible compounds in the hopes of discovering a handful of structures that interact with the target. J.A. 331-32, 381-86; S.A. 2. Or they may narrow the universe of compounds a bit, making educated guesses as to the sorts of untested structures that are most likely to yield results. These screenings of untested structures are conducted in vitro, for it would cost a mint and take an

eternity to screen this volume of variations in animals. J.A. 384; S.A. 2.

If these screenings yield a few especially suitable structures, the drug innovator conducts further experiments to help it decide whether to proceed to the next level of seeking FDA regulatory review, J.A. 331-32, a process that is extensive, expensive, and long—and fraught with uncertainty. J.A. 343-45; Tr. 1257-58. The FDA approval process for a new drug unfolds in two basic phases—the "preclinical phase" and the "clinical phase"—each directed at developing information to support a separate application to the FDA. J.A. 331-34. The preclinical phase involves the development of information to satisfy the FDA that the drug is sufficiently effective and safe to justify testing as an Investigational New Drug, or "IND," in human clinical trials. *See* 21 U.S.C. § 355(i); 21 C.F.R. § 312.23; J.A. 334-36. The information developed in this phase—from conducting experiments in test tubes and animals that can mimic human disease—is presented to the FDA in an IND application (often called an "IND," for short). J.A. 331-33; S.A. 9-10. The gathering of this preclinical information for a drug candidate, and perhaps a few close variations, typically takes three to five years, J.A. 332-33, 343-45, and costs millions of dollars, T. Ex. 70 at 25.

Only if the FDA is satisfied with the extensive preclinical information presented to it may the innovator proceed to the clinical phase, which involves another multiple-year battery of experiments, this time on human subjects. *See* 21 U.S.C. § 355(c)-(e), (i); J.A. 332-33. Upon completion of the clinical phase, the innovator submits its second application to the FDA, a New Drug Application ("NDA"), which is directed at demonstrating that the drug is both safe and effective enough to be approved for sale. 21 U.S.C. § 355(d); J.A. 333, 422. The whole approval process—from the collection of data for an IND application

to ultimate FDA approval—typically takes more than a decade, J.A. 332-33, 339-40, and costs a half a billion dollars, J.A. 343-45.

Regulatory approval of generics. The process for approval of a generic is simpler, speedier, and cheaper. *See* CBO, *supra*, at 43-44. The sponsor of the generic drug does not have to prove, in animal studies or clinical studies, that the drug is safe and effective—for the innovator has already carried that burden—but only that the particular version proposed has the same active ingredient as, and is "bioequivalent" to, the pioneer drug it is mimicking, 21 U.S.C. § 355(j)(2)(A)(iv), which is to say that the body absorbs it and processes it in the same way, *id.* § 355(j)(8)(B). The manufacturer presents this information to the FDA in a one-step application called an Abbreviated New Drug Application ("ANDA"). *Id.* § 355(j).

Scripps, With Merck's Support, Conducts Basic Research To Discover A Potential New Approach To Cancer Therapy

This case presents a classic story line in the progression from basic research to the development, refinement, and regulatory review of a promising new drug. *See* S.A. 1 (timeline). The central character is Dr. David Cheresh of Scripps. Dr. Cheresh is a renowned cancer researcher, D. Ex. 2 at 10-11, who worked in collaboration with Merck, Tr. 2347-55, to develop an innovative approach to curing cancer and then helped Merck generate the data necessary to satisfy the FDA (and European regulatory authorities) that the best drug candidate identified during the collaboration was sufficiently promising and safe to test in humans, J.A. 283-84; Tr. 2033. As a result of the collaborative efforts, human clinical trials had commenced in Europe by the time of trial. J.A. 317-18; Tr. 1287, 1348-49.

In the mid-1980s, Dr. Cheresh began studying the role of special proteins located on the outside surface of certain human cells. J.A. 138; T. Ex. FG at 1; Tr. 1995-96. Those proteins, called "integrins," both anchor the cells in place and communicate with other cells. Tr. 124-28, 818-19, 822-23. Dr. Cheresh focused initially on one of the integrins, "$a_?ß_3$" (pronounced "alpha-v-beta-3"). Tr. 1992-94. He discovered that they are found on the surfaces of cells in sprouting blood vessels. J.A. 138; T. Ex. FG at 1; Tr. 2008-12.

This discovery was of interest to anyone studying diseases that relate to "angiogenesis," the process by which new blood vessels sprout from existing ones. Tr. 1060-61, 1621. Cancer is one such disease. Tr. 1061. Research had revealed that when a small tumor starts forming, it emits chemicals that cause nearby blood vessels to branch out and grow toward the tumor, like a bean sprout toward sunlight, until they form new capillaries that sustain the tumor cells with food and oxygen. Tr. 1058-59. There was reason to believe that stunting the growth of blood vessels could starve the tumor. Tr. 1060-61.

Over the course of more than six years of basic research funded in part by Merck, Tr. 2347-60, Dr. Cheresh found a way to do just that. He started with a special antibody he designed. T. Ex. FG at 1; Tr. 1990, 2000-02. Antibodies are large protein molecules that can be manipulated to bind specifically and tightly to a target, Tr. 1976, and in this case Dr. Cheresh created an antibody that targeted the $a_?ß_3$ surface receptor. T. Ex. FG at 1; Tr. 2000-01. Essentially, the antibody clamps on and envelops a portion of the $a_?ß_3$ surface receptor in a way that blocks it from interacting with other molecules—much like a glob of hardened putty on a doorknob might block a key from getting anywhere near the lock. J.A. 190-91.

The basic research culminated with Dr. Cheresh's successful effort, early in 1994, to block the receptor in a living system with actual blood vessels. S.A. 20. He used a fertilized chicken egg, specifically the part of the egg—called the "CAM" (for chorioallantoic membrane)—where the blood supply to the developing embryo grows. Tr. 1625-26, 2021-32; T. Ex. 26 at 2. He induced proliferation of new blood vessels by placing a tiny tumor directly on the CAM. Tr. 1624-28, 2031-32. He found he could stop the blood vessels from growing toward the tumor by injecting his antibody. Tr. 1628-32, 2031-32. The antibody blocked the magnetic effect of tumors, by jamming the $a_?ß_3$ surface receptors on the cells of growing blood vessels. Tr. 887-89, 1624-32.

Merck Discovers A Simpler Compound With The Same Effect, And Enlists Scripps To Study That Structure

If that were all the Scripps-Merck collaboration had achieved, this patent infringement case would never have been brought. The patents involved in this case say nothing about angiogenesis, antibodies, or cancer treatments. *See* S.A. 11-19.

This suit targets experiments that Scripps scientists conducted, in collaboration with Merck, with a compound that seemed superior to Dr. Cheresh's antibody. Back in Germany, Merck had developed and screened hundreds of chemicals in test tubes, J.A. 384; D. Ex. 2 at 11, in an effort to find a handful that could also jam a blood vessel's surface protein, but in a more targeted manner—more like the tip of a key broken off in the lock than a glob of putty blocking the whole doorknob, Tr. 2146. Out of that screening effort emerged a candidate, which Merck called EMD 66203 (for simplicity, let us call it "EMD-6"). D. Ex. 7 at 34-35. Long before the experiments at issue here, Merck had confirmed that, at least in a test tube, EMD-6 effectively jammed the

$a_?ß_3$ receptor on the surface of blood vessel cells. T. Ex. AAY at 1-5; T. Ex. 17 at 1-9.

Dr. Cheresh tried Merck's EMD-6 in his chicken CAM model, early in 1994. S.A. 20. The results proved equally dramatic. EMD-6 retarded the growth of blood vessels—and it actually shrank the tumors. J.A. 113-16, 269-71. Dr. Cheresh also showed that blocking the $a_?ß_3$ surface receptor with the compound signals the blood vessel cell to self-destruct. T. Ex. 24 at 2-4; Tr. 2033, 2090, 2095. Dr. Cheresh incorporated his discovery about the effect of EMD-6 on blood vessel growth in chicken CAMs into a patent application filed in March, 1994, S.A. 20, and, by May, 1994, he communicated to Merck about the data showing the shrinkage of tumors, J.A. 113-16.

In sum, before the summer of 1994, Merck and Dr. Cheresh had reason to believe that they had a promising cancer drug on their hands. J.A. 113-118, 270-71. As Dr. Cheresh put it in a letter to Merck, in June, 1994, immediately after learning about EMD-6's tumor-shrinking power, "At this time . . . Merck is in a good position to develop peptide based antagonists of angiogenesis for treatment of cancer." J.A. 118.

Merck Enlists Scripps To Conduct Preclinical Studies For An Investigational New Drug Application To The FDA

The complaint in this case originally challenged all these early experiments with EMD-6, but they are not before this Court. *See infra* at 22-23 (explaining District Court's rulings). This case is not about Merck's early screening efforts to identify the EMD-6 structure as the leading inhibitor of the receptor, nor about Dr. Cheresh's initial testing of Merck's compound in test tubes or chicken eggs. This case focuses exclusively on a series of experiments—beginning in August, 1994 and continuing through 1998—all

of which were conducted *after* Dr. Cheresh had discovered that EMD-6 could shrink tumors and after he announced to Merck that they had discovered a potential "treatment of cancer." J.A. 118.

With Merck's continued (and, indeed, expanded) support, Dr. Cheresh conducted a series of experiments to demonstrate the potential for treating cancer safely and effectively with Merck's compound or an analog. J.A 283-98; S.A. 3-8. He supervised essentially the same experiments—on a parallel track, with the support of another drug company—with the antibody he invented. J.A. 160, 270-79.

With both potential drugs, Dr. Cheresh performed some experiments in test tubes to ascertain how well each would bind to the cell surface receptor, and how well each blocks other agents from binding to that receptor, but the main focus of the research after 1995 was on animal studies. J.A. 278-79; S.A. 3-5; *see generally* T. Ex. 698. The vast majority of the Scripps experiments on Merck's drug candidate (and, later, a close analog) involved administering varying doses of it to developing chicken embryos, and observing the effect on blood vessel formation. J.A 285-87; S.A. 3-5. Dr. Cheresh also administered the drugs in mice to observe their effect on their blood vessel development and tumors. J.A. 284-98; S.A. 3-5.

According to the uncontradicted trial testimony, each experiment was designed to demonstrate one or more of the following:

- ***Efficacy:*** How well the drug can be expected to work in curing the target disease.

- ***Mechanism of action:*** How it achieves those results.

- ***Pharmacology:*** The appropriate dose and method of delivery.

- ***Pharmacokinetics:*** The rate at which the drug is absorbed into, and eliminated from, the bloodstream.

- ***Toxicity:*** The negative side effects of the drug at various dosages.

J.A. 228-35, 239, 252-61, 278, 283-98; S.A. 3-8. As the Court of Appeals recognized, there was no evidence—presented affirmatively or by cross examination—to dispute that each experiment currently before this Court was reasonably expected to yield evidence on at least one of these subjects. *See* P.A. 5a-6a (confirming that "these tests assessed… histopathology, toxicology, circulation, diffusion, and half-life of the peptides in the bloodstream," as well as "the proper mode for administering the peptides for optimum therapeutic effect"). In short, the focus of the experiments on EMD-6 reflected a shift from basic discovery to inquiry into how well this particular structure would work as a drug. J.A. 283, 321; Tr. 2032-33, 2196, 2358.

Merck funded the first year's worth of this drug development research under its existing contract with Scripps, a 1988 contract that was due to expire in June, 1995. Tr. 2190. But almost immediately after Dr. Cheresh discovered that EMD-6 shrinks tumors—in the same letter in which he heralded Merck's drug as a potential "treatment of cancer," J.A. 117-18—the parties turned their attention to negotiating a renewed agreement reflecting the shift in orientation from basic research to drug development. J.A. 281-83. Months before the agreement was signed, the parties were discussing a "project at Scripps . . . that would then serve as the basis for potential clinical trials," J.A. 119 (December, 1994), and circulating draft language (ultimately incorporated into contract) reflecting their expectation that Scripps would "begin testing the E.M.D. peptide 66203 [*i.e.,*

EMD-6] . . . for efficacy[,] [p]harmacokinetics and toxicity" and their aspiration that "within the third year clinical trials will begin," J.A. 106; *see* J.A. 200.

The resulting agreement vastly expanded the Merck-Scripps relationship with a view toward "lead[ing] the project as close to clinics as possible." J.A. 126. It called upon Dr. Cheresh to conduct "'necessary experiments to satisfy the biological bases and regulatory (FDA) requirements for the implementation of clinical trials'" with EMD-6 or an analog. J.A. 90; P.A. 5a. The parties reached agreement on all material terms in February, 1995, J.A. 124-25, and formally executed the contract in the summer of 1995, Tr. 2357, shortly before the 1988 agreement expired. J.A. 118.

The 1995 agreement allocated responsibilities to conduct the various sorts of experiments that the FDA considers in deciding whether to allow clinical trials to proceed. J.A. 79-80, 283; Tr. 2358-59; *see also* J.A. 95-107, 119-28. As the Court of Appeals accurately observed, Merck assigned to Scripps the responsibility "to evaluate the specificity, efficacy, and toxicity" of Merck's drug candidates and close analogs, "to explain the mechanism by which these drug candidates work, and to determine which candidates were effective and safe enough to warrant testing in humans." P.A. 5a (partially quoting J.A. 85); *see also* J.A. 95-107, 119-28, 317-18. Under the 1995 agreement, Merck took responsibility for conducting a series of expensive experiments to assess the compound's toxicity and pharmacokinetics under stringent procedures that the FDA describes as "Good Laboratory Practices" ("GLP"). J.A. 93, 313, 315; Tr. 2200. That did not mean that the renowned Dr. Cheresh was guilty of "Bad Laboratory Practices," but only that the formal "GLP" certification was unnecessary for the sort of experiments he was performing. *See, e.g.*, 21 C.F.R. § 312.23(a)(8)(iii) (GLP requirements apply only to

certain sorts of "nonclinical laboratory study"); *id.* § 58.3(d) (excluding from definition of relevant "nonclinical laboratory study" any "exploratory studies carried out to determine whether a test article has any potential utility"); J.A. 168, 443-44, 449-53; *see also* J.A. 166.

Merck agreed to pay Scripps $6 million to conduct the experiments within its assigned areas.[3] J.A 94. As the earlier proposal anticipated, the 1995 agreement did set an ambitious three-year deadline for the completion of these preclinical studies, at which point "an IND will be filed," J.A. 87, and "clinical trials .. . will begin," J.A. 88; *see also* J.A. 283, 311-12, 321. Even if this aggressive deadline had been met, none of the parties expected that any drug could possibly secure FDA marketing approval before 2005, after another seven years of clinical studies, and a combined total of ten years of preclinical and clinical research. S.A. 30.

The research that ensued under the 1995 agreement used EMD-6 or two close cousins, EMD 85189 and EMD 121974, which, for simplicity, will be referred to as "EMD-8" and "EMD-12," respectively. Tr. 847. EMD-8 is so close in structure to EMD-6 that the single difference—a difference of three atoms out of a structure of dozens, J.A. 180—is noticeable only upon close scrutiny. *Compare* S.A. 42 *with* S.A. 43. And EMD-12's active ingredient is structurally identical to EMD-8, the only difference being that it is

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[3] The same agreement provided additional funding for Scripps to assess drug candidates that might mimic Merck's drug. J.A. 67-94. Dr. Cheresh tested at most 15 to 20 possible candidates, none of which was as promising as its lead candidate. J.A. 197, 289, 319; D. Ex. 7 at 37. None of those compounds are covered by the patents at issue in this case.

constituted slightly differently for storage in solution; as used in the laboratory, they are indistinguishable. *Compare* S.A. 43 *with* S.A. 44; Tr. 762-63. (For this reason, references to "EMD-8" in this brief encompass EMD-12, as well.) The experiments at issue in this case involved one of these three compounds; no experiment involved any other allegedly infringing peptide. *See generally* T. Ex. 698.

Dr. Cheresh's preclinical research started out with a focus on the single chemical, EMD-6. Tr. 2221-22. After about a year, Merck asked Dr. Cheresh to switch the focus to EMD-8 and later to its twin EMD-12. Tr. 2222. With two isolated exceptions, none of Dr. Cheresh's experiments after late 1996 used EMD-6. *See* T. Ex. 698. At about the same point, in November, 1996, the results of the preliminary animal studies looked so promising that Merck appointed a formal inter-disciplinary team called an "EPG" (a German acronym translated as Developmental Project Group) to oversee research, regulatory approval, marketing, and manufacturing. J.A. 201-05. This means the company made the tentative judgment that the information developed about the drug candidate was sufficiently encouraging that it justified the further investment of millions of dollars to obtain approval to test the candidate in humans, and eventually to market the drug, provided the preclinical and clinical experiments continued to be encouraging. J.A. 201-05, 207-08, 314-315, 385-86. Simultaneously, Merck formally transferred the animal data on its drug candidate, including all of Dr. Cheresh's earlier animal data, to a specialized computer system, called MEDIS, which reports data in the format the FDA requires. J.A. 207-14, 380-82, 388-89, 391-93.

This case originally involved experiments conducted under the 1995 agreement by two of Dr. Cheresh's colleagues at Scripps, Dr. Martin Friedlander and Dr. Chris Storgard. J.A. 231-33; Tr. 1822-25. Using the same two

variations of Merck's drug, J.A. 232-33, 241-42, they demonstrated in mice and rabbits that the drug had a significant effect on two other diseases—rheumatoid arthritis, J.A. 230-31, and a blinding disease called macular degeneration, Tr. 1853-54—involving abnormal blood vessel growth. *See* J.A. 231-35, 252-60. It is undisputed that every one of their experiments, too, generated data on the same preclinical topics as Dr. Cheresh's—efficacy, mechanism of action, pharmacology, pharmacokinetics, and toxicity. J.A. 231-35, 239-42, 251-60. Their research came to a screeching halt when the verdict in this case came down, so clinical trials never commenced. J.A. 49, 52.

Dr. Cheresh's Data Are Incorporated Into Applications And Draft Reports For Regulatory Review

Dr. Cheresh's experiments yielded exactly the sort of information that is of interest to the FDA. That was the unmistakable opinion of the independent consultants Merck hired in 1997 to assist in preparing an IND application. J.A. 209-14, 261-62; Tr. 2064-65, 2197. As FDA regulatory experts, their job was to assess which data to submit to the FDA, and to prepare summaries of the data to include in Merck's IND application. J.A. 210-12; Tr. 2197. These FDA specialists included in their data summaries the results of all Dr. Cheresh's work with the chicken CAMs and mice on both EMD-6 and EMD-8 (including its identical twin EMD-12). J.A. 133-46, 210-14, 316-17; Tr. 2197. They also summarized the test-tube data. J.A. 145; Tr. 1563-64. By May, 1998, Merck's FDA consultants contacted the FDA with a view toward reviewing the data. J.A. 394-97; T. Ex. 75 at 1-2; *see* 21 U.S.C. § 355(b)(4)(B) (encouraging innovators to schedule one or more "pre-IND meetings" with FDA staff to discuss the research needed and protocols).

Meanwhile, beginning in October, 1998, Merck met with top officials of the National Cancer Institute ("NCI")

and gave them copies of the data summaries for its IND application. J.A. 147-55, 214-17; Tr. 2197. Based on those submissions, the NCI undertook both to shepherd Merck's drug—in the form of EMD-12 (EMD-8's identical twin)—through the FDA's IND process, and to conduct the clinical trials itself. P.A. 28a; J.A 214-17, 221. In other words, the federal government's leading cancer experts made the independent judgment that the Scripps-Merck collaboration had produced exactly the sort of data that would persuade the FDA to permit clinical trials to proceed.

In part because discovery in this litigation closed in late 1998, the jury did not learn what happened next. As the dissent in the Court of Appeals mentions, the record reflects that the NCI *did* in fact file an IND application for EMD-12. *See* P.A. 28a. The record also reflects one other fact the jury never learned: The FDA did, indeed, permit clinical trials to proceed. Docket # 950 at 2.

The trial evidence does reflect that Merck filed a request to commence clinical trials on cancer patients in Europe in 1997. P.A. 28a; J.A. 317-18; Tr. 1287-88. That application was approved as well, and those clinical trials are under way. J.A. 317-18; S.A. 31; Tr. 1287-88.

The trial evidence also reflects what happened on the parallel track with the analogous antibody Dr. Cheresh developed. As of May, 1994, Scripps had licensed the antibody to a small biotech company called Ixsys, in return for its commitment to fund the preclinical research with the antibody. J.A. 271; T. Ex. 29 at 1-3. Like Merck, Ixsys enlisted Dr. Cheresh to supervise studies on efficacy, mechanism of action, pharmacology, pharmacokinetics, and toxicity, J.A. 276-78, but reserved for itself the responsibility to handle the safety studies under GLP conditions, J.A. 278-79.

Ixsys, of course, had every incentive to avoid expensive studies that would have no bearing on FDA approval. J.A. 271-78, 398-407. Yet, there is no dispute that scientists working under Dr. Cheresh's direction conducted essentially the same experiments—in test tubes, as well as in chicken CAMs and mice—with his antibody that he conducted with the Merck compounds. J.A. 156-60, 277-79. Nor is there any dispute that when Ixsys submitted its IND application on the antibody, it included data from all those experiments. J.A. 156-59, 279; Tr. 3048. Nor is there any dispute that the FDA accepted, and relied on, those experiments when it approved the Ixsys IND application in 1997, J.A. 405-07, and cleared the way for clinical trials, J.A. 278-79, 405-07.

This was no coincidence. Long before the IND application was filed, the Scripps researchers had met with FDA officials for advice on what studies would be helpful to its review of this sort of drug. J.A. 273-76, 304-06. The conversations, which began as early as 1996, J.A. 304-06, broadly addressed therapies based both on Ixsys' antibody and on Merck's drugs, J.A. 273-76. And Dr. Cheresh fully understood that the requirements for FDA approval of the antibody and EMD therapies would be very similar, since they shared the same mechanism and effect. J.A. 305-06.

Telios Fails To Discover A Valuable Use Of Its Patented Inventions And Goes Bankrupt

Dr. Cheresh was not, of course, the first to take interest in cell surface proteins, or in the $a_v\beta_3$ surface receptor, in particular. Among the many other scientists in the field were Dr. Erkki Ruoslahti and Dr. Michael Piersbacher of the nearby Burnham Institute in San Diego.

These scientists discovered that a short peptide of three amino acids, called the "RGD peptide" bound especially well to certain cell surface receptors. S.A. 41; Tr. 342. (A protein is a long chain of amino acids, and a peptide is just a

short segment of a protein molecule, which is to say, a few amino acids linked together. Tr. 831.) The Burnham scientists discovered that many protein chains that included within them that particular sequence of three amino acids—represented by the symbols R, G, and D—would bind well to those surface receptors. Tr. 342.

In 1983 and 1985, they filed a series of patents relating to the vast genus of compounds that might include the RGD sequence and various uses of such compounds in living systems. Tr. 380-81. These patents identified only peptides with the amino acids arrayed in a linear chain; it had not occurred to the inventors that the peptides would be more useful when arranged in a tight circular formation, as Merck did in synthesizing its structure. S.A. 11-19; Tr. 1779, 1804-05; *see* S.A. 41.

In 1987, the Burnham Institute, with the backing of outside investors, established a company named Telios Pharmaceuticals, Inc. ("Telios") to hold the license to the patents and exploit them commercially. Tr. 505-09. Telios directed its attention almost exclusively to inducing or preventing cell adhesion—the process by which cell surface proteins help anchor cells in place—with a view toward preventing heart attacks, promoting wound healing, and inhibiting cells from rejecting prosthetic devices. S.A. 11-19. Telios did not focus on how blood vessel growth affects cancer, rheumatoid arthritis, macular degeneration, or any other disease. Tr. 521-24.

Telios spent over $150 million in efforts to develop an RGD peptide product with commercial value. Tr. 394-95. Telios failed. Tr. 512-13. It declared bankruptcy in January, 1995. Tr. 513. In August, 1995, Integra LifeSciences I, Ltd. purchased Telios in a bankruptcy sale for about $20 million. J.A. 175-76; T. Ex. TK.

Telios Sues, Alleging Patent Infringement, After Having Failed To Persuade Merck To Support Its Struggling Projects

With the patents poised to expire within a few short years, between 2003 and 2006, S.A. 11-19, Telios and the Burnham Institute (with Integra joining shortly thereafter) turned to litigation as the only way to wring value from the patented inventions. Telios had tried to persuade Merck to infuse the struggling company with millions of dollars to support its struggling development projects, Tr. 525-27, but it never offered Merck a straight license that would cover the Merck-Scripps collaboration, untethered from such a grand scheme, Tr. 407, 412. *But cf.* P.A. 6a (noting that "Integra offered Merck licenses to the patents-in-suit," without mentioning the offers were linked to a demand for support in developing unrelated drugs). Instead, in July, 1996, these plaintiffs (collectively, "Integra") sued Merck, Scripps, and Dr. Cheresh,[4] claiming that the collaboration violated their patents, because Merck's drug included an RGD peptide. J.A. 27-28.

Integra did not allege that Merck was marketing an infringing product. In fact, there was no way Merck could have brought its drug to market before the patents expired (between 2003 and 2006). S.A. 11-19. Merck projected going to market no earlier than 2005, S.A. 30; Tr. 1410, and by trial it was clear that the early projections were too optimistic, Tr. 2781.

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[4] In recounting the litigation proceedings, these defendants will be referred to collectively as "Merck." At the close of evidence, the District Court dismissed all remaining claims against Scripps and Dr. Cheresh. Tr. 3334-35.

Merck Unsuccessfully Invokes FDA Exemption

Merck asserted that all the experiments were exempt from patent infringement claims: The experiments through the end of 1994—except a single chicken CAM experiment to assess pharmacokinetics in August, 1994—were exempt under the "common law research exemption," also called the "experimental use exception," *see Embrex, Inc. v. Serv. Eng'g Corp.*, 216 F.3d 1343, 1349 (Fed. Cir. 2000), and all the rest of the experiments were exempt under the FDA exemption, T. Ex. A9; *see* Docket # 976 at 12-16. The District Court agreed with Merck's position on the common law research exemption, and granted judgment as a matter of law ("JMOL") as to every experiment through the end of 1994 (except that August experiment), Tr. 3369-75, 3390-91, a ruling that has not been appealed and is not before this Court. But the District Court denied JMOL as to the rest of the experiments under the FDA exemption, concluding that there were disputed issues of fact as to whether the experiments were exempt. Tr. 3375-91.

The District Court submitted the issue to the jury. It defined the FDA exemption as requiring Merck to "prove . . . that it would be objectively reasonable . . . to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question." P.A. 39a; J.A. 57. But instead of directing the jury to decide whether each experiment fell within the safe harbor, the verdict form directed the jury to reject the FDA exemption if it found that *any one* experiment fell outside the safe harbor. J.A. 62 (verdict form asking whether Merck proved "that all of accused activities are covered by the FDA Exemption"); *see* J.A. 454-56 (hearing re defendants' objections to verdict form).

The jury concluded that the experiments infringed at least one Integra patent, and rejected the FDA exemption. J.A. 59, 62; Tr. 3718. But there is no way to tell whether it concluded that all the experiments fell outside the FDA safe harbor, just some experiments, or only one experiment. Tr. 3720. The jury awarded $15 million in damages. P.A. 38a; J.A. 62.

Merck renewed its defense under the FDA exemption in a post-verdict motion for JMOL. Docket # 1048. The District Court denied the motion. P.A. 47a-50a. Even though the court had earlier opined that "much of the evidence at trial established that the accused experiments generated the types of information that are submitted to the FDA," P.A. 40a, it repeated its view that there were disputed issues of fact relating to what information the FDA expects or requires in an IND application. P.A. 48a-49a; *see also* Docket # 1135 at 2 (rejecting motion for new trial on same issue).

The Court Of Appeals Affirms—On A Theory Neither Adopted By The District Court Nor Pressed By Integra

A split panel of the Court Appeals affirmed, over a vehement dissent. P.A. 24a-37a. In contrast to the District Court, the majority did not review the record for material issues of disputed fact. Rather, the panel concluded, apparently as a matter of law, that the FDA exemption *could not* apply to *any* of the experiments remaining in the case. The panel interpreted the words "solely for uses reasonably related to . . . submission of information" to the FDA as a requirement that the activity be "'solely for uses reasonably related' to *clinical tests* for the FDA," P.A. 11a (emphasis added), as contrasted with animal and test-tube experiments that produce information that must be submitted to the FDA before proceeding to human clinical trials. The majority justified this limitation on the ground that "[t]he FDA has no

interest in the hunt for drugs that may or may not later undergo *clinical testing for FDA approval*." P.A. 12a (emphasis added).

The majority did not focus on the language Congress adopted, but instead on the unstated legislative "purposes," derived from references to "generic drugs" in a House Committee report. P.A. 9a. The majority opined that the immediate impetus for the FDA exemption was a Federal Circuit decision, *Roche Prods., Inc. v. Bolar Pharm. Co.*, 733 F.2d 858 (Fed. Cir. 1984), that Congress found untenable. P.A. 9a. In *Roche*, the Federal Circuit held that a researcher infringes a patent by conducting experiments on drug—which happened to be a generic drug—with a view toward generating the data necessary for FDA approval to market the generic once the patent expires. The majority concluded that "the express objective of the 1984 Act was to facilitate immediate entry of safe, effective *generic* drugs into the marketplace upon expiration of a pioneer drug patent." P.A. 12a (emphasis added). Invoking these legislative purposes, the panel further opined that Congress intended that "the 'nature of the interference with the rights of the patent holder' would not be 'substantial,' but 'de minimus [sic].'" P.A. 9a (quoting committee report). Based on these factors, the Federal Circuit rejected "an interpretation of [the safe-harbor provision] that would encompass drug development activities far beyond those necessary to acquire information for FDA approval of a *patented pioneer drug already on the market*"—i.e., beyond the approval of a generic drug. P.A. 13a (emphasis added).

Judge Newman dissented, objecting to the proposition that the "'safe harbor' does not apply to federal registration of pioneering new drugs like the Scripps/Merck products here at issue, but only to registration of generic copies of drugs for which the patent is about to expire." P.A. 32a. She observed both that "the statute has been interpreted as of

broader scope," and that the parties themselves all assumed that the safe harbor covers new drugs, not just generics. *Id*. (quoting *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990)).

The Court Of Appeals Revises Its Opinion

The Court of Appeals denied Merck's petition for rehearing and rehearing en banc. P.A. 53a. Simultaneously, it released an "errata" sheet inserting a few line-edits into its opinion. P.A. 36a-37a. The gist of the edits was captured in one sentence: "While the scope of the safe harbor is not limited to generic drug approval, *see Eli Lilly & Co. v. Medtronic, Inc*., 496 U.S. 661 (1990), the history of the 1984 Act informs the breadth of the statutory test." P.A. 36a. The practical effect of the opinion, however, remained the same, for if a drug innovator cannot conduct the studies necessary to support an IND application for a new drug, it will never reach the NDA stage, and the safe harbor will apply only to generics.

SUMMARY OF ARGUMENT

Congress crafted a broad FDA exemption covering any "use" of a patented product "reasonably related to the development and submission of information" to the FDA. 35 U.S.C. § 271(e)(1). A drug sponsor seeking approval of a new drug must submit information to the FDA first in the form of an IND application, which presents data from animal and test-tube studies to justify clinical trials in humans. By its plain terms, then, the FDA exemption embraces any experiments "reasonably related" to developing information for an IND application. That means that a drug innovator's research falls within the safe harbor so long as it is directed at developing information relevant to an IND application.

The Court of Appeals erred in concluding that the plain language of the FDA exemption must be limited by policy concerns it gleaned from the legislative history. Nothing in the statute's language suggests that the exemption is limited only, or even primarily, to generic drugs, as the Court of Appeals believed. To the contrary, the last time this Court considered the FDA exemption, it emphasized that the exemption covers all drugs, and, indeed, the full range of products subject to FDA approval, from food additives to medical devices. *See Eli Lilly & Co. v. Medtronic Inc.*, 496 U.S. 661, 674 (1990).

Nor was the Court of Appeals justified in reading into the statute nontextual limits based upon the view that Congress intended only a de minimis encroachment on patent rights. Even if this policy gloss could overcome the unambiguous statutory language, it would not support the Court of Appeals' conclusion. No matter how far the FDA exemption extends up the chain of drug development, it would still insulate only laboratory experiments, leaving the patent holder free to reap all economic rewards from marketing the invention for the full term of the patent. In any event, to apply the exemption beyond the clinical phase

in new drug development would not, as the Court of Appeals thought, insulate all general biomedical research and all screening for new drug candidates from patent suits. The FDA exemption could be read to protect the critical stages of drug design and preclinical experiments—which is what the Scripps experiments were—but not basic research or preliminary screening of structures that have never been shown to affect the target.

When the FDA exemption is faithfully applied to the experiments at issue here, each experiment was exempt as a matter of law because (1) they were conducted after the point at which it was reasonable to believe Merck's compound was a viable drug candidate; and (2) the experiments produced information the FDA considers in an IND application.

As to the first point: Merck and Scripps had identified the structure of a compound (typified by EMD-6) that had the demonstrated potential to cure a specific disease (cancer) in an animal model (chicken CAMs) through a known mechanism (by blocking a known receptor to stunt angiogenesis, thereby cutting off the blood supply to a tumor). Nor is there any dispute that by the time Merck undertook the first accused experiment, Merck and Scripps had already begun talking about the research they would need to conduct for FDA approval, or that the formal agreement that emerged from those discussions—in 1995—expressly contemplated that the data would be directed at securing FDA approval for EMD-6 or an analog.

As to the second point: the undisputed testimony was that every single experiment produced data bearing on one or more of the following subjects: safety, efficacy, mechanism of action, pharmacology, or pharmacokinetics. These are the very subjects that are of interest to the FDA in deciding whether an IND application has adequately justified clinical trials in humans.

Beyond that, there is no dispute that the information developed by Dr. Cheresh was included in Merck's draft summaries for the IND application; was used by Merck's FDA consultants to produce their reports; was relied upon by the NCI, the federal government's leading cancer agency, in its decision both to shepherd the IND application through the FDA and to conduct the clinical trials; and was exactly the same type of information included by a different drug company in its parallel IND application for the antibody drug.

ARGUMENT

THE FDA EXEMPTION COVERS THE ACCUSED EXPERIMENTS AS A MATTER OF LAW, BECAUSE EACH WAS REASONABLY RELATED TO PRODUCING DATA FOR AN FDA APPLICATION.

A. The FDA Exemption Covers A Wide Range Of Animal And Test-Tube Research That Is Submitted To The FDA In Connection With Both An Investigational New Drug Application And The Ultimate New Drug Application.

When it came to delivering promising drug therapies to suffering patients, Congress was not stingy. The Patent Act provides that "whoever without authority makes, uses, offers to sell, or sells any patented invention . . . , during the term of the patent therefor, infringes the patent." 35 U.S.C. § 271(a). But with the FDA exemption, Congress immunized any "use" of a patented invention "reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs." 35 U.S.C. § 271(e)(1). In choosing these words, Congress insulated *any* experiment that would yield the "information" from any experiment, so long as it would be reasonable for the researcher to believe the experiment

could generate information of a sort the FDA considers at some point in its role as regulator of drugs.

The language Congress crafted bespeaks no categorical limitations. Congress did not limit the FDA exemption to "information related to generic drugs." Nor did Congress limit the exemption to "information related to clinical studies," or to a particular sort of FDA application, such as an NDA (for *ultimate* approval of a new drug for clinical testing in humans) or an ANDA (for approval of a generic replica of an existing drug).

Certainly, there is no categorical limitation implicit in the exemption's emphasis that infringement is excused "solely for [the] uses" described, and not for other "uses." Contrary to the Court of Appeals' insinuation, *see* P.A. 10a, that adverb offers no assistance in discerning which phases of drug development are covered by the FDA exemption. It means only that a drug innovator's freedom to use a patented invention under the FDA exemption is not a license to infringe in other ways, such as commercial exploitation. *See, e.g., Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269, 1275 (N.D. Cal. 1991), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993).

The Court of Appeals engrafted onto the FDA exemption a limitation nowhere to be found in the statute's words. It converted the requirement that an experiment merely be "reasonably related to the development and submission of information" *to the FDA* into a requirement that the activity be "'solely for uses reasonably related' to *clinical tests* for the FDA," P.A. 11a (emphasis added)—in other words, into a rule that only research directed at the application for *ultimate* FDA approval, the NDA, is within the safe harbor, but research toward the IND application is not. P.A. 12a.

As an initial matter, even by its own terms, the Court of Appeals reached the wrong conclusion, for a myopic focus on the ultimate FDA application—the NDA—does not translate into a focus on clinical testing in humans to the exclusion of preclinical testing in animals or test tubes. When a drug sponsor files its NDA for ultimate approval, the FDA requires not just clinical data, but a full "*[n]onclinical* pharmacology and toxicology section … describing … *animal and in vitro studies* with [the] drug" on such diverse subjects as "the pharmacological action of the drug in relation to its proposed therapeutic indication and studies that otherwise define the pharmacologic properties of the drug," 21 C.F.R. § 314.50(d)(2)(i) (emphasis added), and "the absorption, distribution, metabolism, and excretion of the drug in animals," *id*. § 314.50(d)(2) (emphasis added); *see* 21 C.F.R. § 314.50(d)(2)(v). Moreover, Congress directed the FDA to consider not just "information submitted to [the FDA] as part of the application," but also "any other information before [the FDA] with respect to such drug," including preclinical data presented in the earlier IND application. 21 U.S.C. § 355(c) & (d) . As the FDA puts it, "an NDA is supposed to tell the drug's whole story, including .. . results of the animal studies." FDA, *Benefit vs. Risk: How CDER Approves New Drugs* 2*, available at* http/www.fda.gov/cder/about/whatwedo/testtube-5.pdf [hereinafter "*Benefit vs. Risk*"]; *see* J.A. 338-40.

More importantly, in opining that "[t]he FDA has no interest in the hunt for drugs that may or may not later undergo *clinical testing for FDA approval*," P.A. 12a (emphasis added), and that "[t]he Scripps-Merck experiments did not supply information for submission to the . . . FDA[]," P.A. 10a, the Court of Appeals ignored an undeniable legal reality: The NDA is not the only application that must be submitted to the FDA in connection with its regulation of new drugs. The IND application is a critical prerequisite. *See* 21 U.S.C. § 355(i)(1) . That is why

Integra has never disputed that the FDA exemption covers the collection of information for an IND application, P.A. 33a, which, by statutory and regulatory command, entails the generation and "submission . . . *of preclinical tests (including tests on animals)* of such drug adequate to justify the proposed clinical testing." 21 U.S.C. § 355(i)(1)(A) (emphasis added); *see also id.* § 355(i)(2)(B) (anticipating "primary data tabulations from animal or human studies"); 21 C.F.R. §§ 312.22-312.23.

In light of this requirement, it should be no surprise that in the two decades after enactment of the FDA exemption, every court to have grappled with the exemption's scope concluded that it covered new drugs, not just generics; IND applications, not just NDAs; and preclinical research (or research even further down the chain), not just clinical research.[5] As one of the earliest opinions (in the analogous

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[5] *See Nexell Therapeutics, Inc. v. Amcell Corp.*, 199 F. Supp. 2d 197, 204 (D. Del. 2002) (activities conducted to solicit clinicians to enter into FDA-approved clinical trials are exempt because such a "use" would contribute to generating information that is likely relevant to the FDA approval process); *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, No. 95 Civ. 8833 (RPP), 2001 WL 1512597, at *6 (S.D.N.Y. Nov. 28, 2001) (use of patented intermediates for developing drug analogs is exempt because it relates to a preliminary activity that may be useful in generating information that could be submitted to the FDA); *Amgen, Inc. v. Hoechst Marion Roussel, Inc*., 3 F. Supp. 2d 104, 110 (D. Mass. 1998) (safe harbor protects animal testing conducted to assess a drug's safety for clinical tests because the animal tests were "calculated to lead to relevant information for submission" to the FDA, even though results were never submitted); *cf. Telectronics Pacing Sys., Inc. v. Ventritex, Inc.*, 982 F.2d 1520, 1523 (Fed. Cir. 1992) (trade show displays of medical devices to solicit clinical investigators for clinical trials were exempt activities because

(Footnote continued)

context of pre-clinical testing of medical devices) put it, "because safety certification . . . was necessary in order to obtain import approval and conduct clinical tests, the . . . tests necessary to obtain that certification would have to be considered reasonably related to the generation of data for submission to the FDA." *Intermedics*, 775 F. Supp. at 1284. The Federal Circuit had affirmed this view, leaving drug innovators like Merck, and researchers like Dr. Cheresh, confident that they could rely on the statutory language and perform preclinical studies on new drugs without fear of having to defend a patent infringement suit.

B. The Court Of Appeals Erred In Limiting The FDA Exemption's Plain Language Based On Legislative History and Policy Rationales.

In reversing its previous stance and overturning two decades' worth of settled expectations, the Court of Appeals scarcely paused to reflect on the words Congress chose, and never focused on the information the FDA considers in assessing either an IND application or an NDA. Instead, it vaulted from a block quote of the FDA exemption directly to the unstated legislative "purposes," as reflected in a House report. P.A. 9a-10a. From this source, the Court of Appeals derived two limiting principles reflected nowhere in the statute's language: that Congress' primary concern was generic drugs and that any encroachment on patent rights must be de minimis. P.A. 9a. These limiting principles led

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"device sponsors are responsible for selecting qualified investigators and providing them with the necessary information to conduct clinical testing").

the Court of Appeals to conclude that: (1) the FDA exemption is limited mainly to generic drugs; (2) for new drugs, the exemption applies mainly (perhaps exclusively) to clinical research on humans, not to research leading up to that clinical phase; and (3) any broader application threatens to devalue a specific category of patents not at issue here—so-called "research tool" patents—in derogation of the interest in de minimis effect on patent rights.

The short answer to each of these conclusions is that purported congressional purposes and policy ramifications in other contexts cannot amend the clear language Congress chose to enact. *See Am. Tobacco Co. v. Patterson*, 456 U.S. 63, 68 (1982). The longer answer, presented below, is that each conclusion both misconstrues the congressional purpose and misapprehends the nature of drug research.

1. As this Court has already held, Congress did not intend to limit the FDA exemption only, or even mainly, to generic drugs.

The overarching theme of the opinion below—both before and after the court's revisions—is that "the express objective of the [FDA exemption] was to facilitate the immediate entry of safe, effective *generic* drugs into the marketplace upon expiration of a pioneer drug patent." P.A. 12a (emphasis added); *see* P.A. 36a (erratum adds, "the history of the 1984 Act informs the breadth of the statutory test"). The objective was "express[ed]," the Court of Appeals believed, not in the statute—which expresses no such thing—but only in the legislative history. That expression, alone, led the Court of Appeals to conclude that the exemption does not embrace "drug development activities far beyond those necessary to acquire information for FDA approval of a *patented pioneer drug already on the market*"—which is to say, approval of a generic drug. P.A. 13a (emphasis added).

In the Court of Appeals' view, Congress had intended to say that the safe harbor protects manufacturers of generic drugs that mimic products already on the market, but the protection does not extend (or rarely extends) to an innovator prepared to spend tens of millions to test a pioneer drug that could be a more effective cure, or that could be safer, than any drug on the market. Put another way, the FDA exemption gives the least protection to drugs with the greatest social value and the longest regulatory delays. The Court of Appeals offered no reason why any Congress would have wanted to codify such a perverse result, much less why a court should be permitted to redraft Congress' handiwork to achieve that result when Congress indicated the opposite in the words it chose.

The last time this Court considered the FDA exemption, in *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990), it rejected any effort to extract a limit on the statutory language from the legislative history. This Court, there, faced a thornier question of statutory construction: whether the FDA exemption "is a limited exception which applies *only to drugs*, . . . or applies generally to patented inventions, including medical devices." *Eli Lilly & Co v. Medtronic, Inc.*, 872 F.2d 402, 405 (Fed. Cir. 1989) (emphasis added), where Congress referred only to the submission of information "*under a Federal law* which regulates the manufacture, use, or sale of drugs."

Even though there was no clear answer, the Court rejected the invitation to focus on the purpose reflected in the legislative history. 496 U.S. at 669 n.2, 670 n.3. As the Court put it:

> [The patent holder's] principal argument is that the legislative history of [the FDA exemption] mentions only drugs—which is quite different, of course, from saying (as it does not) that only drugs are included. "It is not the law that a statute can have no effects

> which are not explicitly mentioned in its legislative history . . . ."

Id. at 669 n.2 (citation omitted). As this passage illustrates, throughout its analysis, the Court presumed that the FDA exemption applied with equal force to all drugs—new drugs and generic drugs, alike. *See id.* at 671, 674-75. But for present purposes, the point is a more modest one: If the legislative history is too inconsequential to help resolve an ambiguity, then it certainly cannot overcome unambiguous statutory language.

In a related vein, this Court also refuted the related argument—echoed by the Court of Appeals, here, as well—"that it was 'the 1984 *Roche* decision' which prompted enactment" of the FDA exemption, and the safe harbor should therefore be limited to overruling that precedent. *Id.* at 670 n.3; *see* P.A. 9a ("The second reason for the 1984 Act responded to this court's decision in *Roche* . . . ."). The argument there, as here, was that the reach of the FDA exemption ought to be limited to reversing *Roche*'s holding, narrowly construed here to apply patent laws to FDA-related experiments on *generics*. The Court allowed that "[u]ndoubtedly, the decision in *Roche* prompted the *proposal* of [the exemption]; but whether that alone accounted for its *enactment* is quite a different question," which the Court answered in the negative. 496 U.S. at 670 n.3 (emphasis in original).

This Court's analysis in *Lilly* is undoubtedly why the court below never explicitly held that the FDA exemption is available only to generics—the only conclusion that would flow naturally from its analysis—but merely that it cannot apply to "drug development activities *far beyond* those necessary to acquire information for FDA approval of" a generic. P.A. 13a (emphasis added). What qualifies as "far beyond" generic approval—as opposed to "just beyond" or

"fairly beyond"—is anyone's guess, as is the question why gathering information for approval for "medical devices, food additives, color additives, . . . antibiotic drugs, and human biological products," is not "far beyond" the pale, *Lilly*, 496 U.S. at 674, while producing information in support of an IND application for a new drug is. Whatever the explanation, the Court of Appeals reached a conclusion that is not only countertextual and counterintuitive, but resistant to rational application.

2. Applying the FDA exemption faithfully to preclinical research does not unduly extend the safe harbor to embrace all general biomedical research or drug discovery, and, however interpreted, still amounts to a de minimis encroachment on patent rights.

A second theme coursing through the Court of Appeals' opinion is that reading the statutory language as written, to embrace preclinical research reasonably related to the IND application, is tantamount to saying that the exemption "globally embrace[s] *all experimental activity* that at some point, however attenuated, may lead to an FDA approval process," P.A. 13a (emphasis added), or that the "safe harbor reaches back down the chain of experimentation to embrace [any] development and identification of new drugs," P.A. 10a. This, the Court of Appeals believed, would violate either the unwritten proscription against extending the FDA exemption too "far beyond" the generic context or the uncodified interest in limiting the exemption to de minimis effect. P.A. 13a.

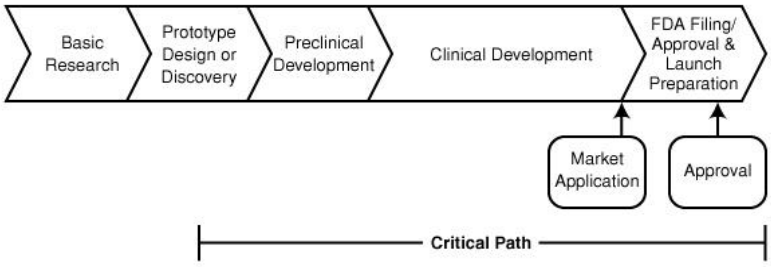
To take the latter point first, when the House committee observed that "'*the nature of the interference* with the rights of the patent holder' would not be 'substantial,' but 'de minimus [sic],'" P.A. 9a (quoting H.R. Rep. No. 857, at 8, *reprinted in* 1984 U.S.C.A.N.N. 2684, 2692) (emphasis added), it explained why: "The patent holder retains the

right to exclude others from the major commercial market place during the life of the patent." H.R. Rep. No. 857, at 8, *reprinted in* 1984 U.S.C.A.N.N. at 2692. The committee's point was that the FDA exemption authorizes little beyond experiments to gather information, with no expectation of making a penny of profit until after, probably long after, the patent expires.

Viewed in this way, the FDA exemption impinges only on the patent holder's claimed "right" to stall the progress of medical research and delay the delivery of promising therapies to patients (thereby securing for itself an unfair patent-term extension). In other words, the infringement *is* de minimis just as Congress intended—no matter how far "back down the chain of experimentation" the exemption reaches. P.A. 10a. That is why at least one court has had no trouble concluding that all drug research is, indeed, "reasonably related" to the development of information headed toward the FDA. *See Rhone-Poulenc Rorer,* 2001 WL 1512597, at *6.

But this Court need not go that far to decide this case. As the Court of Appeals correctly observed, all the "research conducted under the Scripps-Merck agreement" was "pre-clinical research." P.A. 10a. Extending the exemption beyond the clinical phase—to cover preclinical research, or even a few steps before—is not tantamount to insulating all drug research from the patent laws. The FDA graphically illustrated the point in a recent white paper describing the phases of drug development:

Figure 4: The Critical Path for Medical Product Development



FDA, *Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* 16 (March 16, 2004), *available at* http://www.fda.gov/oc/initiatives /criticalpath/whitepaper.html (emphasis added); *see, e.g.,* S.A. 1, 2. As this spectrum illustrates, the FDA exemption can "reach[] back down the chain of experimentation to embrace" preclinical development, and even further back in the "Critical Path" toward drug development—to efforts to optimize the design of promising drug candidates—without embracing "all experimental activity that at some point . . . may lead to an FDA approval process." It is inaccurate to view drug research, as the Court of Appeals did, as a binary universe, breaking down into (1) clinical research and (2) everything before it. And it is equally inaccurate to label everything before the clinical trials "general biomedical research to identify new pharmaceutical compounds," P.A. 12a; *see* P.A. 14a ("general biomedical experimentation"), or "exploratory research that may rationally form a predicate for future FDA clinical tests," P.A. 13a.

This spectrum manifests itself in the researcher's shifting orientation. A university scientist conducting basic research on the cause and progression of a disease is unlikely to think of his experiments as directed at the FDA. Nor would a researcher who, having learned of a plausible

mechanism of a disease, screens compounds whose structures are not known to be (or reasonably suspected of being) likely to affect the disease, in the hopes of finding one that might do so. These scientists might dream of some day discovering a blockbuster drug, but they are under no delusion in those early years that the FDA is the audience.

Everything changes when a researcher endures the unpredictable and open-ended process of screening untested structures and emerges with unmistakable evidence that a particular structure shows promise, in a living body, in treating a particular disease through a known mechanism. After that point, the researcher may continue to optimize the drug candidate's structure, testing variations to ascertain which shows the greatest promise with the fewest side effects or complications. J.A. 358, 416-20. In fact, the FDA fully expects the scientist to conduct such research on "related drugs," and to include the resulting information in the IND application, if it sheds light on the lead candidate's suitability. 21 C.F.R. § 312.23(a)(5)(v); *infra* at 45. But from that juncture, every experiment that bears on the relationship between the drug candidate or its analogs and the target disease is reasonably viewed as pertinent to the FDA—at least to the extent that the experiment relates to a topic that is of interest to the FDA. While a drug innovator that has crossed this crucial threshold could never be sure *ex ante* that a particular drug candidate will emerge as *the* candidate for commercial development, or that a specific experiment will necessarily find its way into an IND application, there can be no doubt that the prospect of regulatory approval is very much in the picture.

The difference in orientation manifests itself in marked, and objectively verifiable, differences in behavior. At the most fundamental level, the experiments, themselves, change in character. The final stages of drug design and preclinical testing are marked by an increasing (though not exclusive)

emphasis on vastly more expensive and time-consuming animal tests. S.A. 2; J.A. 384-85. Accordingly, the decision to undertake these experiments is a business decision made typically by a team of scientific, medical, regulatory, and business personnel within a pharmaceutical company, in a process that draws upon the data and expertise of the scientists conducting the general biomedical research and the ones screening compounds or engaged in preliminary drug design, as well as regulatory scientists, medical doctors, and pharmacologists. J.A. 201-05, 322-26.

If the drug continues to look promising as the research progresses, several events may unfold (as they did in this case): Multi-disciplinary teams of scientific, clinical, and regulatory experts are appointed to shepherd the candidate through the regulatory approval process and into the clinics. J.A. 201-08, 381-89. Data management and preservation become highly formalized, precisely because every experiment conducted is viewed as potentially relevant to the FDA. J.A. 207-09, 380-81, 388-89, 391-93. Consultants with expertise in navigating the FDA's IND application process are contacted to help design the right experiments and report the data compellingly. J.A. 208-09, 396-97. And informal conversations with FDA personnel begin. J.A. 276-77, 353-57.

There is, in short, a world of difference between basic exploratory research or screening of untested structures in test tubes and the drug optimization and preclinical research, mostly on animals, that drug innovators conduct with a view toward demonstrating (in an IND application to the FDA) that clinical trials are justified. "Preclinical" does not embrace every imaginable experiment before the clinical phase, any more than "prepubescent" embraces infants and fetuses.

3. The limited ramifications of this case for research tools do not justify abandoning the FDA exemption's plain language.

Equally misplaced was the Court of Appeals' final policy concern, that a faithful reading of the FDA exemption "would swallow the whole benefit of the Patent Act for some categories of biotechnological inventions." P.A. 14a. What the court had in mind was one category of invention, research tools, and it was wrong about them.

Research tools are inventions that assist a scientist in conducting research. Scientists could use research tools in any context, not just drug research. *See* NIH, *Office of Technology Transfer, Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources: Final Notice* 9, *available at* http://ott.od.nih.gov/RTguide_final.html (defining research tools) (last visited Feb. 13, 2005). In the pharmaceutical context, examples of research tools might be a centrifuge, a dripless pipette, a cell line, or a special assay for screening compounds on the basis of certain properties. *See* NIH, *Report of the NIH Working Group on Research Tools* 3 (June 4, 1998), *available at* http://www.nih.gov/news/researchtools/ (defining research tool to include "laboratory equipment and machines," as well as "cell lines, monoclonal antibodies, reagents, animal models," and the like). The Court of Appeals' concern was this: If the FDA exemption means that a drug researcher may infringe any patent, so long as the purpose is to garner information about drugs candidates, then the researcher can freely infringe not just patents on pharmaceuticals, but also patents on centrifuges, pipettes, and a wide range of biological assays—so long as the invention is used in an experiment about a drug candidate.

Initially, it bears emphasis that this case does not present the research tool question. Integra has never argued before

the lower courts that the accused experiments fell outside the safe harbor because they infringed research tool patents. That was no oversight: The accused experiments used patented compounds and patented methods of using the compounds with a view toward bringing a drug to market upon expiration of the patents. In other words, in this case the patented inventions were the subject of the research, not just a tool used to study that subject. And that was the sole basis on which Integra litigated this case.

In any event, for several reasons, the research tool dilemma offers scant assistance in resolving the question of statutory construction now before this Court. First, the research tool issue exists (or not) without regard to how the Court resolves the question of statutory construction presented here. If some subset of research tool patents can be infringed freely by drug researchers, it is because the statute refers broadly to "uses reasonably related to the development . . . of information" headed for the FDA—not because the exemption covers activities before the clinical phase, as Merck urges here.

Second, any danger of devaluing research tool patents is limited. No drug researcher would opt to build himself a new centrifuge or blow his own dripless pipettes—infringing the patents of others just because he thinks the FDA exemption would let him get away with it. Even as to patented biological products or processes that a researcher could reproduce in the lab, the harm can extend no further than the scope of the FDA exemption. If the FDA exemption were read, for example, not to cover basic research or the screening of untested structures, the research tools would have their full value in those research contexts. Tellingly, in the 20 years in which the courts and, thus, the scientific community, understood the FDA exemption to cover preclinical studies (and much more), only one reported case has emerged in which a drug innovator invoked the

exemption to claim the right to infringe a patent that could even arguably be called a research tool patent. *See Rhone-Poulenc Rorer*, 2001 WL 1512597 at *6.

Third, if ever such a case emerged, it is not at all clear that use of the research tool would be exempt. A lower court could construe the language of the FDA exemption to apply only in circumstances where the "use" of "a patented invention . . . develop[s] . . . information" for submission to the FDA *about that patented invention*, but not in situations where the use of the patented invention (the research tool) develops information but about something else (an unpatented drug candidate). Or a court might conclude that the use of a patented research tool is not "reasonably related" to the development of information for the FDA where equivalent data about the drug or the disease in question could easily be developed through other means, or perhaps where the research tool has no relationship to the disease under study.

The universe of research tools is so diverse and practices are changing so dramatically that the legal issue of how the FDA exemption relates to research tools cannot be answered in the abstract. All we can know for sure is that any court confronting this issue would benefit from a fully developed factual record, and rounds of focused legal argument. Meanwhile, the possibility of a marginal encroachment on research tool patents has little bearing on whether Congress, in 1984, intended to insulate preclinical experiments from patent infringement claims.

C. The Undisputed Evidence Confirms That All The Accused Experiments Were Directed At Producing Data Reasonably Related To An Investigational New Drug Application.

The primary disputes below were not over whether the FDA exemption's plain language should be limited in light

of congressional purposes, and certainly not around whether the generation of information for an IND application is protected; these arguments were largely innovations of the Court of Appeals. The litigation, as shaped by the parties, revolved around two topics: (1) whether the research had progressed to the point where a reasonable drug innovator in Merck's position could have considered the FDA a likely audience for the research; and (2) whether Dr. Cheresh's experiments produced data of the sort that was of interest to the FDA. Based upon undisputed evidence, both questions must be answered in the affirmative.

1. Once Merck's drug shrank tumors in an animal model, it was objectively reasonable to view the FDA as an audience for the ensuing research.

There can be no dispute that Dr. Cheresh and his colleagues at Scripps conducted the experiments in question after the point at which it would have been objectively reasonable for Merck and Scripps to believe they had their hands on a promising drug for treatment of a specific disease. The point could not have been any later than March, 1994—five months before the first of the accused experiments and more than three years before the last. J.A. 113; S.A. 20-21. By that point, Merck had identified the structure of a compound (a cyclic peptide typified by EMD-6) that had the demonstrated potential to cure a specific disease (cancer) in an animal model (chicken CAMs) by blocking a known target (the $\alpha_v\beta_3$ receptor on the surface of growing blood cells) through a known mechanism (by blocking the receptor to stunt angiogenesis, thereby cutting off the blood supply to a tumor, starving it, and making it shrink). Simply put, when a compound shrinks a cancerous tumor in an animal model, it is a promising drug candidate.

This does not necessarily mean that Merck knew at that moment that EMD-6 would be the *exact* compound it would bring to clinical trials, with no further refinement. Drug

companies rarely have that level of certitude when they fix their eyes on the approval process. J.A. 357-58. Nor, obviously, did it mean that the evidence in support of EMD-6 was so definitive that Merck knew for sure it could cure cancer, and all other diseases involving abnormal blood vessel growth, and was ready to shut down all research on parallel tracks. It means only that the research on this structure had progressed to the point where it was reasonable to begin generating data with an eye toward the FDA approval process.

That is all the FDA exemption requires. FDA regulations demand not only data on the particular compound proposed, but also, as relevant, data on "related drugs." 21 C.F.R. § 312.23(a)(5)(v). Moreover, there is nothing in the FDA exemption to suggest that the protection evaporates if the drug sponsor pursues the risky prospect of FDA approval of a drug while continuing to explore back up drug candidates in parallel. While the Court of Appeals characterized the experiments as "general biomedical research to identify new pharmaceutical compounds," P.A. 12a; *see* P.A. 14a ("general biomedical experimentation"), and "exploratory research," P.A. 13a—labels that the FDA and the broader scientific community would consider inapt, *see supra* at 39-40—there can be no question that it was objectively reasonable for Merck and Dr. Cheresh to believe, when they conducted this research, that it would be of interest to the FDA.

For proof that Merck and Dr. Cheresh, in fact, harbored the belief that the time had come to cast an eye toward the FDA—if any such proof is necessary under the FDA exemption's objective standard—one need look no further than their correspondence in the immediate aftermath of the discovery: (1) the June, 1994 letter from Dr. Cheresh opining that "[a]t this time . . . Merck is in a good position to develop peptide based antagonists of angiogenesis for

treatment of cancer," J.A. 118; (2) the December, 1994 letter memorializing discussions about "a sizable increase in the support of this project … that would then serve as the basis for potential clinical trials," J.A. 119; (3) the February, 1995 research proposal (eventually appended to the 1995 agreement) memorializing their intention that Scripps would "begin testing the E.M.D. peptide 66203 . . . for efficacy[,] [p]harmacokinetics and toxicity" and "within the third year clinical trials will begin," J.A. 106; and (4) the 1995 agreement, ultimately calling for Scripps to conduct "necessary experiments to satisfy the biological bases and regulatory (FDA) requirements for the implementation of clinical trials," J.A. 90; Tr. 2397; *see supra* at 14. All of this transpired a year or two before Integra's lawsuit materialized, and the context furnishes further support for what is objectively evident: Merck had a drug candidate that was sufficiently promising that further research to establish its suitability for clinical testing was justified.

2. Dr. Cheresh's experiments produced information on a variety of topics relevant to an IND application.

Concededly, just because a compound appears to be a promising drug candidate does not entitle the drug innovator to do anything with the candidate; the use must be of a sort that is reasonably likely to generate data that the FDA would be interested in considering.

The question of what information the FDA deems relevant to an IND application is not a question of fact, but a question of law, capable of resolution simply by reading the FDA's regulations. While a primary focus of the IND application is to verify that the proposed human testing is "reasonably safe," 21 C.F.R. § 312.23(a)(8), the FDA requires evidence also that "the compound exhibits pharmacological activity that justifies commercial development." FDA, *IND Review Process* 4, *available at*

http://www.fda.gov/cder/handbook/ind.htm (last visited Feb. 14, 2005); *see* J.A 333-36, 400, 439. At the broadest level, FDA regulations require the sponsor of a new drug to present "[t]he rationale for the drug or the research study." 21 C.F.R. § 312.23(a)(3)(iv). The rationale must necessarily rest upon data—from experiments in both animals and test tubes—demonstrating the basis for believing that the drug might have therapeutic value in a particular disease. J.A. 334, 416-17, 439; *see* FDA, *Benefit vs. Risk*, *supra*, at 2. No drug sponsor could get away with the following "rationale": "This chemical does not poison mice too badly and it would be nifty to see how badly it poisons humans."

Beyond that, the FDA regulations demand that an IND application include "[a]dequate information about *pharmacological* and toxicological studies of the drug *involving laboratory animals or in vitro*," 21 C.F.R. § 312.23(a)(8) (emphasis added), including "[a] section describing the . . . *mechanism(s) of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug,*" *id.* § 312.23(a)(8)(i) (emphasis added); J.A. 335, 440-41. The regulations also require the applicant to submit a draft "Investigator's Brochure," 21 C.F.R. § 312.23(a)(5), which includes evidence of "the pharmacological . . . effects of the drug in animals," *id.* § 312.23(a)(5)(i), and the "pharmacokinetics and biological distribution of the drug in animals," *id.* § 312.23(a)(5)(ii). *See supra* at 12-13 (defining those terms).

The FDA's regulations refer not only to animal studies, but also to "studies of the drug . . . *in vitro*" as a basis for proving "that it is reasonably safe to conduct the proposed clinical investigations." *Id.* § 312.23(a)(8). In fact, the FDA has advised researchers that "[m]any drugs thought to be of potential value in treating human disease are introduced into development based on knowledge of in vitro receptor binding properties"—exactly the sorts of in vitro

experiments at issue here—in addition to "identified pharmacodynamic effects in animals." FDA, *Guidance for Industry Exposure-Response Relationships—Study Design, Data, Analysis, and Regulatory Applications* (Apr. 2003), *available at* http://www.fda.gov/cber/gdlns/exposure.htm; *see* FDA, *Benefit vs. Risk, supra*, at 8 (defining "preclinical studies" as "[s]tudies that test a drug on animals and other nonhuman test systems").

To summarize, in order to proceed to clinical trials with a view toward ultimately securing FDA approval to market its promising new drug candidate, Merck had to conduct preclinical studies, in both animals and test tubes, providing "[a]dequate information about *pharmacological* . . . studies of the drug *involving laboratory animals or in vitro*," 21 C.F.R. § 312.23(a)(8) (emphasis added); *see id.* § 312.23(a)(5)(i); describe "the pharmacological effects and *mechanism(s) of action of the drug in animals*, and information on the *absorption, distribution, metabolism, and excretion of the drug," id.* § 312.23(a)(8)(i) (emphasis added); and furnish studies on "the pharmacokinetics and biological distribution of the drug in animals," *id.* § 312.23(a)(5)(ii) (emphasis added). And it had to provide this information not only on the particular compound proposed, but also, as relevant, on "related drugs." *Id.* § 312.23(a)(5)(v).

That is exactly what the accused experiments yielded. There has never been any dispute that the experiments in question developed information on one or more of these topics with respect to two close cousins (and a structurally identical variant of one). *See* J.A. 231-35, 239-41, 250-51, 252-64, 284-98; Tr. 1860-62. The Court of Appeals acknowledged as much when it recited, as undisputed fact, that the purpose of the experiments was "to evaluate the specificity, efficacy, and toxicity of [the three versions] for various diseases, to explain the mechanism by which these

drug candidates work, and to determine which candidates were effective and safe enough to warrant testing in humans." P.A. 5a. To observe, as the Court of Appeals did, that every one of "these tests assessed the action of the [Merck drugs], including the histopathology [*i.e.*, its effect on diseased tissue], toxicology, circulation, diffusion, and half-life [the rate of elimination] . . . in the bloodstream," and "examined the proper mode of administering the [drugs] for optimum therapeutic effect," P.A. 5a-6a, is to recognize that these experiments had to have been "reasonably related to the development and submission of information" in connection with an IND application, for every single one of those topics is of interest to the FDA in deciding whether to allow human trials to proceed. Any reasonable drug innovator would undertake this sort of research before filing an IND application. J.A. 332-44, 351-58, 398-407.

Undisputed evidence further confirms that this information was of interest to the FDA in reviewing an IND application, even though the jury did not get the chance to see the ultimate IND application that the NCI submitted. Not only did Merck include the data in its draft summaries for its IND application, J.A. 209-12, 260-61, but third parties with no stake in this case verified, through their own conduct, that this information was of exactly the sort that would justify clinical testing. First, Merck's FDA consultants believed that all the Cheresh data should be featured in summary reports that would accompany the IND application. J.A. 209-12. Second, these experiments persuaded the NCI to sponsor the clinical research and assume the role of preparing the final draft of the IND application and shepherding it through the FDA. J.A. 147-55, 214-17. Third, on a separate track, another drug innovator (Ixsys) made the independent judgment to have Dr. Cheresh oversee a virtually identical battery of experiments, and to include the results when it submitted its IND application seeking FDA approval to conduct clinical

trials on a parallel drug (Dr. Cheresh's antibody). J.A. 271-77, 398-406; Tr. 3048. The FDA's decision to approve that IND application speaks volumes about the legitimacy and relevance of the data before it. J.A. 277, 405-07; Tr. 1375.

In sum, the FDA's regulations specify what subjects the agency is interested in exploring. The experiments at issue all yielded information on exactly those subjects. And there is no dispute that the information did in fact find its way into documents that were FDA bound. The FDA exemption protects all the experiments as a matter of law.

CONCLUSION

The ruling of the Court of Appeals should be reversed with directions to enter judgment for Merck on the ground that the FDA exemption insulates the accused experiments from patent infringement liability.

Respectfully submitted,

Donald R. Dunner
Thomas H. Jenkins
FINNEGAN, HENDERSON,
FARABOW, GARRETT &
DUNNER, L.L.P.
901 New York Avenue, N.W.
Washington, D.C. 20001
(202) 408-4000

February 15, 2005

E. Joshua Rosenkranz
Counsel of Record
M. Patricia Thayer
James N. Czaban
Gina M. Parlovecchio
Nishita Doshi
HELLER EHRMAN WHITE &
MCAULIFFE LLP
120 West 45th Street
New York, NY 10036
(212) 832-8300

APPENDIX:

ADDITIONAL STATUTORY PROVISIONS & REGULATIONS

Application Process for New Drugs, 21 U.S.C. § 355:

(b) Filing application; contents

(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use . . . .

* * *

(i) Exemptions of drugs for research; discretionary and mandatory conditions; direct reports to Secretary

(1) The Secretary shall promulgate regulations for exempting from the operation of the foregoing subsections of this section drugs intended solely for investigation use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs. Such regulations may, within the discretion of the Secretary, among other conditions relating to the protection of the public health, provide for conditioning such exemption upon—

(A) the submission to the Secretary, before any clinical testing of a new drug is undertaken, of reports, by the manufacturer or the sponsor of the investigation of such drug, of preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing. . . .

FDA Regulations, 21 C.F.R.:

§ 58.3. Definition[] [of Nonclinical Laboratory Study]

* * *

(d) Nonclinical laboratory study means in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety. The term does not include studies utilizing human subjects or clinical studies or field trials in animals. The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test article.

§ 312.22. General principles of the IND submission.

* * *

(d) … Sponsors are expected to exercise considerable discretion, however, regarding the content of information submitted in each section, depending upon the kind of drug being studied and the nature of the available information.

§ 312.23. IND content and format.

(a) A sponsor who intends to conduct a clinical investigation subject to this part shall submit an "Investigational New Drug Application" (IND) including, in the following order:

* * *

(3) Introductory statement and general investigational plan.

* * *

(iv) A brief description of the overall plan for investigating the drug product for the following year. The plan should include the following: (a) The rationale for the drug study; (b) the indications to be studied. . . .

* * *

(5) Investigator's brochure. If required under § 312.55, a copy of the investigator's brochure, containing the following information:

(i) A brief description of the drug substance and the formulation, including the structural formula, if known.

(ii) A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.

(iii) A summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.

* * *

(v) A description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs. . . .

* * *

(8) Pharmacology and toxicology information. Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations.

(i) Pharmacology and drug disposition. A section describing the pharmacological effects and mechanism(s) of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug, if known.

(ii) Toxicology.

(a) An integrated summary of the toxicological effects of the drug in animals and in vitro.

* * *

(iii) For each nonclinical laboratory study subject to the good laboratory practice regulations under Part 58, or, if the study was not conducted in compliance with the good laboratory practice regulations in Part 58, if the study was conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

§ 314.50. Content and format of a[] [New Drug] [A]pplication.

* * *

(d) Technical sections. The application is required to contain the technical sections described below.

* * *

(2) *Nonclinical pharmacology and toxicology section.* A section describing, with the aid of graphs and tables, animal and in vitro studies with drug [sic], including the following:

(i) Studies of the pharmacological actions of the drug in relation to its proposed therapeutic indication ….

(ii) Studies of the toxicological effects of the drug as they relate to the drug's intended clinical uses ….

* * *

(iv) Any studies of the absorption, distribution, metabolism, and excretion of the drug in animals.